DECLARATION UNDER 37 C.F.R. 1.132		
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	First Inventor	NAGAE
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	Examiner	Sharareh, Shahnam J.
	Docket #	P07336US00/BAS

Commissioner for Patents
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1. I, Tsuneyuki Nagae, am one of the named inventors on the above-identified patent application. I hold a Medical Doctor and Ph. Doctor degree from Tokyo Medical University and am currently employed at the Tokyo Medical University, Tokyo Japan Shinjuku-ku. Therefore, I am one skilled in the art.

2. I am familiar with the present patent application and have studied the outstanding Office Action, prior Office Action and cited prior art.

3. The present invention as recited in claim 3 (Currently Amended) is directed to a novel and non-obvious method of using Photodynamic Therapy (PDT) to suppress the vascular intima in the blood vessel wall and vascular restenosis of the blood vessel which are inducible after angioplasty treatment wherein before or after angioplasty treatment, mono-L-aspartylchlorin e6 is administered intraveniously, followed by irradiating the compound at a time point of 0.5-6 hours after the administration of the e6 compound using a laser at a wavelength at 664 nm at a laser fluence of 1-10 J/cm^2.

4. The prior art of Aizawa et al. U.S. Patent No. 5,308,861 (hereinafter Aizawa) individually or in combination with Narciso Jr. U.S. Patent No. 5,298,018 (hereinafter Narciso) fail to teach or suggest the presently claimed method.

5. Aizawa is specifically directed to only a Photodynamic Therapy (PDT) and in no way suggests PDT is applicable for use contemporaneously with or subsequent to an angioplasty treatment. Moreover, one of ordinary skill in the art would not be motivated by the disclosure of Aizawa to use it's photodynamic method in conjuction with or

subsequent to an angioplasty treatment. Specifically, it would not have been obvious to one of ordinary skill in the art to use its photodynamic method subsequent to an angioplasty treatment because Aizawa does not use a photodynamic treatment in response to treating a mechanical injury, e.g. one resulting from angioplasty as discussed in the present specification. On the contrary, Aizawa is merely directed to the use of photodynamic therapy to treat atherosclerosis in mammals but in no ways does Aizawa teach or suggest the use of photodynamic therapy to treat mechanically injured arterial vessels. Further, Aizawa uses an e6 compound to liberate cytoxic siglet oxygen and to kill SMC cells.

6. Narciso is directed at a Photodynamic Therapy (PDT) used in conjunction with Percutaneous Transluminal Coronary Angioplasty (PTCA) in which a photosensitizer is administered repeatedly over a period of five to eighteen days, followed by a procedure of occluding a blood vessel using a catheter and a final photosensitizing agent administration followed by radiation procedure. Thus, Narciso does not teach PDT during PCTA. Rather, Nacisso clearly teaches PCTA is conducted anywhere from five to eighteen days after PDT. Further, Narciso uses an e6 compound as a competitive inhibitor to inhibit a growth factor of injured SMC cells.

7. Neither Aizawa nor Narciso teaches that the restenosis of the blood vessel induced after an angioplasty procedure can be successfully inhibited using a single administration of NPe6 at a significantly reduced dosage of 0.1-5 mg/kg before or after the angioplasty procedure and by using intravascular irradiation of laser light of 664 nm at a significantly reduced laser fluence of 1 - 10 J/cm^2 by means of a completely inflated balloon of a intravascularly inserted catheter, resulting in a complete interception of the blood stream flowing between the completely inflated balloon of the catheter and the inner wall of the blood vessel, in accordance with claim 3 (Currently Amended). Therefore Aizawa individually or in combination with Narciso fails to teach or suggest the claimed invention.

8. Further, the present invention provides unexpected and advantageous effects not taught or suggested by the prior art, individually or in combination with one another. For

example, the present specification includes data in the form of examples and tables which demonstrate that the present method provides features and advantages which are surprising and not obvious in view of the prior art.

9. For example, in the experiments of Example 2 at pages 35-40 of the present application, the procedure comprising the repetition of the operations of inserting a balloon catheter into an artery vessel of rabbits, inflating the intravascularly inserted balloon of the catheter and drawing out the catheter while keeping the balloon inflated as described at page 35, lines 6-14 of the present application is a procedure which imitates the angioplasty procedure which produces the intervented and angioplasty-injured sites of the blood vessel.

10. Prior to this imitative angioplasty procedure, in Example 2, NPe6 was administered intravenously at a dosage of 2.5 mg/kg (see page 35, lines 4-6 of the present application). In this regard, the whole procedure of Example 2 may appear to deviate, in exact details, from the present method as defined claim 3 (Currently Amended). However, the NPe6 as administered intravenously prior to the imitative angioplasty procedure was conducted so that the NPe6 could be taken up by the angioplasty-injured site of the blood vessel and could accumulate selectively in the injured site and continue to selectively accumulate and remain within the injured site, and thus the NPe6, as administered, behaves in the same way as when NPe6 is intravenously administered at the dosage of 2.5 mg/kg just after the imitative angioplasty procedure.

11. In Example 2, as described at page 37, lines 17-27 of the present application, in accordance with the method of claim 3 (Currently Amended), the flow of the bloodstream between the outer wall side of the completely inflated balloon and the inner wall side of the blood vessel was intercepted completely at the balloon-injured site, namely the angioplasty-injured site of the blood vessel. At this time, although not explicitly disclosed but actually produced and inherent in such a procedure, the cross-sectional area of the vascular lumen at the angioplasty-injured site of the blood vessel was increased significantly by the inflated balloon, as compared with the original cross-

sectional area of the vascular lumen which could be observed at a time prior to the complete inflation of the balloon.

12. Thereafter, the PDT procedures with the intravascular irradiation of laser light was conducted as described page 37, lines 3-7 as well as at page 37, the last line to page 38, line 9 of the present application. At the end of two weeks after the PDT procedure, it could be observed, in fact, that the PDT-treated site of the blood vessel having received the PDT with the completely inflated balloon of the balloon catheter and with the intravascular laser irradiation via the completely inflated balloon in accordance with the presently claimed invention, continued to have the cross-sectional area of the vascular lumen which was once increased significantly larger than the aforesaid original cross-sectional area of the vascular lumen which was previously observed before the complete inflation of the balloon of the intravascularly inserted balloon catheter, (data not disclosed in Example 2 of the present application).

13. Although, the present Specification does not disclose the additional meritable effect of increasing the cross-sectional area of the vascular lumen which is attainable according to the present method noted in paragraph 12 above, the meritable effect of increasing the cross-sectional area of the vascular lumen is very remarkable, advantageous, and an unexpected effect of the present method, which is entirely unpredictable and unexpected from the cited prior art references of Aizawa and Narciso.

14. Furthermore, referring to the experimental results of Table 1 at page 39 and the descriptions at page 40, lines 1-14 of the present application, when the injured site of the treated group (but comparative) had been treated by the PDT procedure with using the conventional type of cylindrical optical fiber device at a laser fluence of 100 J/cm^2 for the intravascular laser irradiation, there was obtained a poor outcome of a low rate of 28.7% for the inhibition of the neo-intima formation, due to the therapeutic effect of PDT being adversely affected under an attenuation of the laser intensity induced by the influences of the light absorption by the bloodstream flowing around the laser-emitting optical fiber within the vascular lumen. Moreover, this poor outcome of the low rate of 28.7% for the inhibition of the neo-intima formation varies among the experiments.

Consequently, when the treated group in accordance with the present invention had been treated by the PDT procedure using the completed inflated balloon of the intravascularly interposed balloon catheter and effecting the laser irradiation only at a half-reduced laser fluence of 50 J/cm^2 for the intravascular laser irradiation, a superior outcome was obtained in terms of a higher rate of 44.3% for the inhibition of the neo-intima formation which is obtainable and consistent in every experiments. The consistent positive results obtained using the present method with regard to the rate (%) of the inhibition of the neo-intima formation is remarkedly advantageously to a degree of about 1.5 times (44.3/28.7) using only 50 J/cm^2, as compared with the comparative, treated group which had been treated at 100 J/cm^2 with the use of the conventional type of the laser-emitting optical fiber device, is to be appreciated, and an unexpected result, contrary to the Examiner's allegation in the final Office Action.

15. Further, a series of additional experiments for carrying out the restenosis-inhibiting method according to the claim 3 (Currently Amended) have been conducted.

16. The procedures of the Example 2 of the present application were repeated but in a modified manner such that the intravenous administration of NPe6 was made before or after the angioplasty procedure set forth on page 35, in lines 3-11 of the Example 2; that the dosage of NPe6 was changed to 1 mg/kg, 2.5 mg/kg and 5 mg/kg, respectively; that the laser fluence for the intravascular laser irradiation via the completely inflated balloon was changed to 1 J/cm^2 and 10 J/cm^2, respectively; and that at the end of 2 weeks after the PDT procedure, there were measured the cross-sectional area (mm^2) of the vascular lumen at the angioplasty-injured site to be treated, as well as the cross-sectional area (mm^2) of the formed neo-intima in the blood vessel at the injured site so treated by PDT; and that the cross-sectional views of the angioplasty-injured site of the blood vessel as observed for the control rabbit not treated with the laser irradiation of the PDT procedures or as observed after the PDT procedure were photographed in colors.

17. The results of the additional series of the experiments are summarized as shown in Table A below.

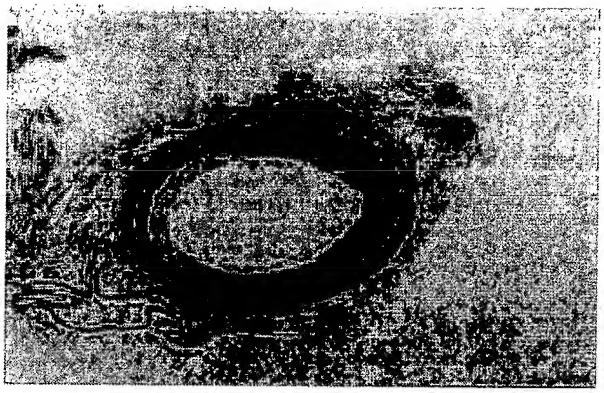
Table A

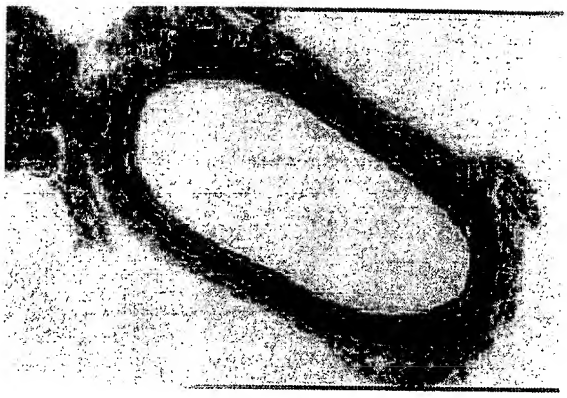
	Laser fluence ($1/cm^2$)	Dose (mg/kg) of NPe6	Lumen area , (mm^2)	Neo-intima area, (mm^2)
Control without PDT (n=7)	0	5	1.11 ± 0.16	0.30 ± 0.04
PDT treated group (n=6)	1	5	1.71 ± 0.05	0.04 ± 0.03**
PDT treated group (n=3)	10	5	2.76 ± 0.77*	0.00 ± 0.00**
PDT treated group (n=6)	10	2.5	2.68 ± 0.45*	0.04 ± 0.04**

*:P<0.05, **:P<0.01

18. It can be observed from Table A above that the cross-sectional area of the vascular lumen at the PDT-treated site was increased by about 2.5 times according to the method of claim 3 (Currently Amended), as compared with the control rabbit which was not treated by the intravascular laser irradiation (in the control rabbits), for instance, when NPe6 was administered at a dosage of 5 mg/kg with or without the intravascular laser intravascular laser irradiation being effected at a laser fluence of 10 J/cm^2.

19. The color photograph of the cross-sectional view of the vascular lumen at the angioplasty-injured site of the control rabbits (not treated by the laser irradiation of the PDT procedure) is shown below in left hand, and the color photograph of the cross-sectional view of the vascular lumen at the PDT-treated site of the rabbits after the PDT procedure made according to this invention is shown below in right-hand.





These further series of the experiments demonstrate that the intravenous administration of NPe6 at a dosage of 0.1 -5 mg/kg, preferably 1-5 mg/kg of NPe6 and the intravascular laser irradiation at a considerably reduced laser fluence of 1-10 J/cm^2 upon the intravascular laser irradiation to the site to be treated according to this invention are sufficient and effective to inhibit the restenosis of the blood vessel inducible after the angioplasty treatment, and also to co-currently increase remarkably the cross sectional area of the vascular lumen at the PDT-treated site greatly much than the initial cross-sectional area of the lumen at the injured site which is not treated by PDT.

20. The combination of the technical features or technical elements as recited in claim 3 (Currently Amended) is clearly unpredictable from Aizawa and Narciso, either alone or in combination. That the inhibition of a restenosis of the blood vessel inducible after the angioplasty procedure can be achieved with success according to claim 3 (Currently Amended) of the present application is entirely unexpectable by one of ordinary skill in the art from the teachings of Aizawa and Narciso.

21. It is declared by the undersigned that all statements made herein of undersigned's own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or

imprisonment, or both, under 18 U.S. Code § 1001, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

February 10, 2006
Date

Tsuneyuki Nagae